iJRASET
International Journal For Research in Applied Science and Engineering Technology



INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 13 **Issue:** VIII **Month of publication:** August 2025

DOI: https://doi.org/10.22214/ijraset.2025.73632

www.ijraset.com

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 13 Issue VIII Aug 2025- Available at www.ijraset.com

Itraconazole Revival: Unlocking Its Anticancer Potential

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Abstract: Itraconazole is an antifungal drug that is a member of the triazole class of medications. It works by preventing the manufacture of ergosterol, which is an essential part of fungal cell membranes, which interferes with the structure and function of the membranes. However, more research is required to fully establish its efficacy and the best treatment regimens for various cancer types. Itraconazole may have anti-cancer properties, especially against cancers like non-small cell lung cancer, prostate cancer, and basal cell carcinoma. Studies have shown potential benefits in inhibiting tumor growth and progression by targeting the Hedgehog signaling pathway.
Keywords: Itraconazole, Triazole, Anti-cancer, Hedgehog signaling pathway.

I. INTRODUCTION

Itraconazole, a triazole antifungal that was synthesized in 1980, was the product of target-oriented drug design after a screening research program that sought to develop a broad-spectrum antifungal agent with proven in vivo activity against molds (including *Aspergillus*), yeasts (*Candida spp.*), and dermatophytes (including *Microsporum canis*). Itraconazole has been in use for almost 30 years and is available in intravenous and oral (capsule and solution) formulations worldwide. Internal data shows that itraconazole has been used to treat over 250 million patients, indicating a well-defined safety profile and generally good tolerance. (1)

Itraconazole binds to plasma proteins substantially (99.8%) and is lipophilic. More clinically significant than the free drug concentration is the itraconazole concentration that is bound to proteins or tissues. Tissues include the kidney, liver, bone, stomach, spleen, and muscle have high itraconazole concentrations despite significant plasma protein binding. Additionally, itraconazole builds up in areas like the skin, nails, lungs, and female reproductive tract that are vulnerable to fungal infections. (1)

A common antifungal drug, itraconazole has shown promise in treating cancer. It has been shown to reverse chemoresistance caused by P-glycoprotein, modify the signal transduction pathways of Hedgehog, a mechanistic target of rapamycin, and Wnt/β-catenin in cancer cells, inhibit angiogenesis and lymph angiogenesis, and potentially disrupt interactions between cancer and stromal cells. Clinical trials have demonstrated the survival advantage of combination treatment for relapsed non-small cell lung, ovarian, triple negative breast, pancreatic, and biliary tract cancers, as well as the clinical benefits of itraconazole monotherapy for prostate cancer and basal cell carcinoma. (2)

II. REPURPOSING ITRACONAZOLE AS A MEDICATION TO FIGHT CANCER

Treatment with itraconazole showed no effect on EOC cells, but it did reduce endothelial cell growth in a dose-dependent manner. Hedgehog, mTOR, and angiogenesis suppression were linked to the antiproliferative impact of endothelial cells. Mice treated with a combination of itraconazole and paclitaxel showed significantly lower tumor weights than the control, paclitaxel-alone, or itraconazole-alone groups in xenograft models of EOC employing SKOV3ip1 or HeyA8. In addition to having a far lower microvessel density than tissue from the other groups, the tissue produced from these tumors also showed inhibition of the mTOR and hedgehog pathways. It was verified these effects in two models of the EOC PDX. (3)

Itraconazole prevented Cutaneous squamous cell carcinoma (cSCC) cells from proliferating, caused apoptosis, and stopped their cell cycle. 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1) and acyl-CoA synthetase long-chain family member 4 (ACSL4) were shown to be markedly increased in A431 cells treated with itraconazole, according to a combined transcriptome and proteomic analysis.

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In A431 cells, itraconazole's antiproliferative effect was reversed by HMGCS1 silencing. The dual-luciferase test demonstrated that itraconazole could increase the transcription of HMGCS1. In A431 cells, HMGCS1 silencing reduced ACSL4 expression. Itraconazole enhanced the amount of ROS, lipid peroxidation, and iron buildup. Furthermore, in A431-bearing animals, itraconazole treatment inhibited tumor growth. Itraconazole is thereby shown to suppress the growth of cSCC by controlling the HMGCS1/ACSL4 axis. (4)

Although ITC release was more maintained by M-ITC-LNC, LNC formulations demonstrated a comparatively small size (43–46 nm) and good entrapment effectiveness (>97%). When compared to ITC-sol and ITC-LNC, cytotoxicity experiments showed that M-ITC-LNC had noticeably higher anticancer activity and selectivity for MCF-7 breast cancer cells. In vivo results after a 14-day therapy of mouse mammary pad Ehrlich tumors supported this pattern. The largest improvement in ITC-induced tumor growth inhibition, proliferation, and necrosis was observed in M-ITC-LNC.The superiority of M-ITC-LNC in boosting the ITC antiangiogenic, apoptotic, and Hedgehog pathway inhibitory actions was confirmed at the molecular level by the tumor content of Gli 1, caspase-3, and vascular endothelial growth factor. Lastly, histopathological and biochemical examination showed that M-ITC-LNC significantly reduced ITC systemic toxicity. The impact of MFS on the structural and release characteristics of LNC, in addition to its unique bioactivities, was responsible for the superior performance of M-ITC-LNC. To sum up, MFS-modified LNC offers a straightforward nanoplatform that combines the advantages of LNC and MFS to improve the chemotherapeutic effectiveness of ITC and potentially other cancer medications. (5)

In esophageal squamous cell carcinoma and adenocarcinoma cell lines, itraconazole caused G1-phase cell-cycle arrest and suppressed cell proliferation. We discovered that itraconazole decreased the phosphorylation of protein kinase AKT in OE33 esophageal cancer cells using an unbiased kinase array. In esophageal cancer cells, itraconazole also reduced the phosphorylation of upstream PI3K, transcriptional expression of the upstream receptor tyrosine kinase HER2, and downstream ribosomal protein S6. Both siRNA-mediated HER2 knockdown and lapatinib, a tyrosine kinase inhibitor that targets HER2, inhibited the development of cancer cells in vitro. In mice whose esophagi and tumors contained measurable amounts of itraconazole and its main metabolite, hydroxyitraconazole, itraconazole markedly suppressed the growth of OE33-derived flank xenografts. Xenografts from mice treated with itraconazole showed lower levels of HER2 total protein and phosphorylation of AKT and S6 proteins than xenografts from mice treated with a placebo. Itraconazole reduced the phosphorylation of AKT and S6 proteins in tumors and the expression of the HER2 total protein in patients with esophageal cancer in an early phase I clinical trial (NCT02749513). These findings show that itraconazole, in part by blocking HER2/AKT signaling, has strong antitumor effects in esophageal cancer. (6)

Itraconazole has the potential to significantly reduce the growth of stomach cancer cells. When combined with 5-FU, itraconazole dramatically slowed the rate at which cancer cells proliferated. Furthermore, itraconazole may cause stomach cancer cells to undergo apoptosis and control the G1-S transition. In samples of human gastric cancer, Hh signaling was aberrantly stimulated. Itraconazole monotherapy administered orally has been shown in in vivo trials to decrease xenograft growth and to dramatically increase the antitumor activity of the chemotherapeutic drug 5-FU. (7)

The findings showed that patients with colon cancer treated with itraconazole had a considerably greater 5-year survival rate. Furthermore, itraconazole caused cleaved caspase-3 expression and G1 cell cycle arrest in COLO 205 and HCT 116 cells, while also reducing viability and cell colony formation. Notably, itraconazole increased the expression of p62 and LC3B, which in turn caused autophagy. The viability of itraconazole-treated COLO 205 and HCT 116 cells significantly increased after LC3 knockdown. All things considered, the current study's findings imply that itraconazole may benefit colon cancer patients, and that the underlying molecular mechanisms of this medication may be linked to the stimulation of autophagic cell death. (8)

The distribution of cholesterol in the intracellular compartments following itraconazole treatment was comparable to that observed following treatment with U18666A (cholesterol transport inhibitor), according to Filipin staining. Phosphatidylserine levels in CaSki cells significantly decreased, but lysophosphatidylcholine levels increased, according to LC/MS analysis. In conclusion, itraconazole changed the phospholipid composition and prevented cholesterol trafficking. Itraconazole's anticancer action may be enhanced by changes in the cell membrane. (9)

The synthesized ITR nanoparticles had a regulated drug release profile, a narrow polydispersity index (PDI), a tiny particle size, and a positive zeta potential. After being exposed for 24 hours, ITR nanoparticles (NPs) were more harmful to H1299 cancer cells than the ITR solution. When compared to the ITR solution, the apoptosis of cancer cells exposed to ITR nanoparticles was also increased. At the molecular level, ITR NPs were superior to ITR solution in promoting pro-apoptotic p53 and Bax while decreasing the production of anti-apoptotic Bcl2 protein. Cells were arrested at the G0/G1 and G2/M phases of the cell cycle more successfully by ITR NPs than by ITR solution. At the molecular level, ITR NPs were superior to ITR solution in promoting pro-apoptotic p53 and Bax while decreasing the production of anti-apoptotic Bcl2 protein.

Cells were arrested at the G0/G1 and G2/M phases of the cell cycle more successfully by ITR NPs than by ITR solution. Thus, encapsulating itraconazole in PLGA NPs coated with chitosan is a potentially effective way to treat lung malignancies. (10)

By causing G1 phase arrest and autophagy-mediated apoptosis in A375 and A2058 cells, itraconazole suppressed the growth of melanoma cells. Moreover, itraconazole inhibited Hedgehog signaling and prevented the recombinant human Sonic Hedgehog (rhShh), a hedgehog agonist, from activating. In the A375 and A2058 xenograft models, itraconazole dramatically slowed tumor growth in vivo. (11)

All of sensitive and resistant lymphoma cell lines were consistently shown to be strongly, specifically, and dose- and time-dependently inhibited by itraconazole. Cells exposed to itraconazole in vitro had G2 cell cycle arrest and a decrease of mitochondrial membrane potential. When paired with different chemotherapeutic drugs, such as doxorubicin, dexamethasone, cisplatin, and different generations of proteasome inhibitors (bortezomib, carfilzomib, or ixazomib), it greatly increased the anti-tumor impact of itraconazole in both RSCL and RRCL. Studies using immunoprecipitation and Western blot showed that HKII binds less to the mitochondrial protein VDAC after being exposed to itraconazole. When HKII was completely silenced (via HKII siRNA interference), the intraconazole-induced decrease of mitochondrial membrane potential was restored. (12)

Both in vitro and in vivo, itraconazole prevents glioblastoma cells from proliferating. Notably, itraconazole treatment causes glioblastoma cells to undergo autophagic progression, and that autophagy blocking significantly reverses the antiproliferative effects of itraconazole, indicating that autophagy has an anticancer effect in response to itraconazole treatment. Functional investigations showed that itraconazole decreased SCP2 levels, which in turn suppressed AKT1-MTOR signaling, induced autophagy, and ultimately inhibited cell proliferation by delaying the transport of cholesterol from late endosomes and lysosomes to the plasma membrane. (13)

Itraconazole caused cell cycle arrest and death, inhibited cell invasion and migration, in a time and dose dependent manner, decreased OSCC cell proliferation and colony formation. It also inhibited tumor development, decreased Ki-67 expression, and triggered apoptosis in the OSCC PDX model. Recombinant human sonic hedgehog protein (rSHH) can be used to reverse the inhibition of oral squamous cell carcinoma cells' migration and proliferation caused by itraconazole's downregulation of the hedgehog pathway's protein expression. (14)

In instances with lymph node involvement, immunohistochemical expression of α-SMA and TF-β was noticeably higher. Itraconazole had a significant interaction with the PI3/AKT proteins. TSCC cell line invasion and migration were inhibited in vitro by ITZ as it considerably decreased migration and invasion capabilities as well as α-SMA, TF-β, SNAIL, and VEGF expressions compared to the control group. (15)

By inducing apoptosis, itraconazole prevents the proliferation and invasion of Ishikawa cells. It dramatically increased the suppression of tumor invasion, which is linked to TAM polarization, when paired with ICis. ITZ promoted the polarization of TAMs from the M2 to the M1 phenotype, decreased IL-10 levels, and boosted FN-γ secretion. Mechanistically, ITZ suppressed Wnt/β-catenin signaling in TAMs by downregulating the expression of Wnt-3α and β-catenin and pregulating Axin-1. Together, ITZ and ICis decreased tumor weight and volume in vivo, repressed Wnt/β-catenin signaling, and changed TAM polarization toward the M1 phenotype. (16)

In order to find an appropriate PDGFRA inhibitor and reduce the time needed for toxicity screening, a molecular docking study was conducted on the chosen antifungal and antineoplastic medications against GISTs based on the docking affinity of human platelet-derived growth factor receptor alpha (PDGFRA) with these medications. Using the AutoDock (AD) and AutoDock Vina (ADV) open-source software, the protein and ligand-binding affinity against POGFRA was examined for thirty-six antifungal medications and five FDA-approved antineoplastic medications. Out of all the medications that were computationally examined, it was expected that itraconazole would be a better PDFRA inhibitor based on the docking score and inhibition constant (K). (17)

Itraconazole and 6-AZA-UTP, FDA-approved medications, were found to be possible B3GALT5 enzyme inhibitors using molecular docking research. According to biological testing on pancreatic cancer cell lines AsPC-1 and MIA PaCa-2, both substances markedly decreased cell viability. By reducing SSEA-3 expression, both medications successfully inhibited the activation of the B3GALT5 enzyme, according to flow cytometry data. Additionally, both compounds demonstrated strong anti-tumor actions by causing pancreatic cancer cells to undergo apoptosis and preventing cell adhesion, colony formation, and migration. Notably, neither medication had any harmful or carcinogenic effects and showed good ADMET profiles. (18)

Itraconazole (ITZ) is a compound that can effectively re-sensitize drug-resistant LNCaPR and C4-2BR prostate cancer cells to DTX treatment, according to an objective drug screen. It can re-sensitize a variety of DTX-resistant cell types, including docetaxel-resistant breast cancer cells as well as cells derived from prostate cancer, including PC-3 and DU145. Expression of the ATP-binding cassette (ABC) transporter protein ABCB1, often referred to as P-glycoprotein (P-gp), is required for this action.

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It also binds firmly to the inward-facing version of ABCB1, which prevents DTX from being transported, according to molecular modeling of ITZ bound to ABCB1. Therefore, ITZ might offer a workable method for re-sensitizing DTX-resistant cells, extending the treatment's beneficial effects on men with metastatic castration-resistant prostate cancer. (19)

Itraconazole and osimertinib work in concert to decrease migration and proliferation, increase apoptosis in osimertinib-resistant cells, and successfully stop the growth of tumors resistant to osimertinib. By promoting the proteasomal breakdown of sonic hedgehog (SHH), itraconazole and osimertinib work together to inactivate the SHH/Dual-specificity phosphatase 13B (DUSP13B)/p-STAT3 and Hedgehog pathways, which in turn suppresses the Myc proto-oncogene protein (c-Myc). Furthermore, DUSP13B modifies the phosphorylation of the signal transducer and activator of transcription 3 (STAT3) through interaction. It's interesting to note that through the SHH/DUSP13B/p-STAT3 signaling axis, SHH overexpression partially restores the synergistic effects of this combo treatment approach. Furthermore, osimertinib resistance is found to be significantly predicted by SHH, (GLI1), p-STAT3, and DUSP13B. p-STAT3 has a negative correlation with DUSP13B and a positive correlation with SHH in lung cancer. These findings collectively demonstrate the critical function of itraconazole in reversing acquired resistance to osimertinib and offer a scientific justification for the combination of osimertinib and itraconazole as a treatment approach. (20)

Itraconazole inhibits EV-mediated pro-metastatic morphological alterations, including colon cancer cells' migratory behavior, via interfering with Rab7's ability to bind to ORP3–VAP-A complexes. While the ICZ moieties that cause antifungal activity and disruption of intracellular cholesterol distribution were eliminated, the VOR complex was still inhibited by new, smaller chemical medications. Given that EVs derived from cancer cells determine the pre-metastatic niche and that cancer cells take over their microenvironment, small-sized inhibitors of the nuclear transfer of EV cargo into host cells may find use in cancer therapy, especially when combined with direct targeting of cancer cells. (21)

Vesicles with a zeta potential of 41.06 ± 2.62 mV, a size of 210.23 ± 6.43 nm, and an entrapment effectiveness of 73.65 ± 1.76% were revealed by the optimized ITZ-HA-GLY. On the A549 cell line, ITZ-HA-GLY also showed a significantly lower IC50 of 13.03 ± 0.2 µg/mL than ITZ suspension (28.14 ± 1.6 µg/mL). Additionally, compared to ITZ suspension, the biodistribution analysis showed a 3.64-fold increased concentration of ITZ-HA-GLY in the lung tissues. Additionally, the mean resistance time of ITZ-HA-GLY decreased more slowly with 14 hours than that of ITZ suspension, indicating that ITZ accumulates inside the lungs and that it may be used as a viable target for lung disease treatment. (22)

C1GALT1 acts by O-glycosylating the pivotal Hedgehog (Hh) signaling component Smoothened (SMO), thereby stabilizing SMO and stimulating the Hh pathway, which directly activates *EWSR1:FLI1* transcription. Itraconazole, an FDA-approved anti-fungal agent that is known to inhibit C1GALT1, reduces EWSR1::FLI1 levels in Ewing sarcoma (ES) cell lines and suppresses growth of ES xenografts in mice. (23)

Significantly, itraconazole prevented Bel-7405 and HepG2 cells from proliferating. Furthermore, it was found to decrease MMP, increase ROS generation, stop the cell cycle, and trigger apoptosis in HepG2 cells. Furthermore, itraconazole also reduced the proliferation of HCC cells and induced apoptosis by activating the death receptors, ROS, AKT/mTOR/S6K, Wnt/catenin, and Hh pathways. Ultimately, we conclude that itraconazole reduces the risk of liver cancer and may be used as a novel treatment for the disease in clinical settings. (24)

The widespread use of itraconazole in the treatment of cancer, however, has been limited by its powerful suppression of the drug metabolizing enzyme cytochrome P450 3A4 (CYP3A4). In an effort to abolish the CYP3A4 inhibition while keeping its antiangiogenic effect, a variety of derivatives in which the 1,2,4-triazole ring is substituted with various azoles and nonazoles were synthesized. With an IC50 of 73 nM and no discernible impact on CYP3A4 (EC50 > 20 µM), 15n with tetrazole instead of 1,2,4-triazole demonstrated the best suppression of human umbilical vein endothelial cell proliferation among these analogues.15n inhibited AMPK/mechanistic target of rapamycin signaling and produced the Niemann-Pick C phenotype (NPC phenotype), just like itraconazole did. These findings indicate that 15n is a promising angiogenesis inhibitor that works well with the majority of other anticancer medications already on the market. (25)

III. DRAWBACKS OF USING ITRACONAZOLE TO TREAT CANCEROUS GROWTHS

Numerous research conducted in the last few years have demonstrated that itraconazole has anti-tumor properties. However, the data on particular medications is frequently very limited due to the lack of big randomized controlled research. The suppression of human hepatocyte CYP3A4, the primary cytochrome P450 in the human liver, is a significant drawback of itraconazole as a new anticancer drug. About 50% of prescribed medications, including the majority of anticancer medications, are metabolized by CYP3A4, a major xenobiotic metabolizing enzyme with important pharmacological and toxicological effects. Changes in catalytic activity are crucial for bioavailability and drug-drug interactions.

Tyrosine kinase inhibitors, which are mostly metabolized by cytochrome P450, are among the majority of anticancer medications whose metabolism is blocked by CYP3A4 inhibition. Therefore, a number of adverse effects that may result from the suppression of CYP3A4 in the liver should be taken into account when using itraconazole in conjunction with other anticancer medications. Additionally, new itraconazole analogs that maintain their antiangiogenic properties with or without CYP3A4 suppression must be developed. Vulnerable populations, such those undergoing targeted immunotherapy or immunosuppressed individuals, may be at risk when using itraconazole medication. According to a study, itraconazole can lower blood IgE and IgG levels by reducing systemic immunological activation. Furthermore, with certain combo treatments, itraconazole may be antagonistic in nature.By blocking rituximab-mediated intracellular calcium influx and preventing CD20 from being recruited to lipid rafts, rituximab in combination with itraconazole antifungal therapy has been shown to reduce the anti-lymphocytic effects of rituximab both in vitro and in vivo. This eliminates the cytotoxic effects of therapeutic antibodies against molecules related to lipid rafts. (2)

IV. PERSPECTIVES FOR THE FUTURE

After being exposed to cytotoxic treatments, the remaining tumors usually exhibit stemness or include cancer stem cells (CSCs). According to a hypothesis, CSCs—which are distinguished by their capacity for self-renewal, multidifferentiation, and chemoresistance—can explain metastasis and recurrence after chemotherapy treatment. Other possible mechanisms that could underlie chemotherapeutic resistance include niche cell protection, latent cell cycles, and multidrug resistance transporters. To increase survival rates and avoid cancer relapse, the development of CSC-targeted therapy is currently the main emphasis. More preclinical research on CSCs and the surrounding stroma cells is necessary since itraconazole may be a promising treatment for CSCs in relapsed disease of several cancer types. ClincalTrials.gov (https://clinicaltrials.gov/ct2/home), UMIN-CTR Search Clinical Trials (http://www.umin.ac.jp/ctr/index.htm), and Google search were used to find ongoing clinical trials including itraconazole (as an anticancer treatment) (Table III). The EU Clinical Trial Register (https://www.clinicaltrialsregister.eu/ctr-search/search) did not have any active clinical trials listed. To explore and characterize novel targets in the tumor and the microenvironment, as well as to find biomarkers predictive of patient response for future enrichment clinical trials, it is crucial to obtain cancer tissues and blood from patients both before and after itraconazole treatment. (2)

V. CONCLUSION

Nowadays, repurposing medications is rapidly gaining popularity in the medical industry. Compared to creating new treatments, the technique saves time and money. This is the situation with itraconazole. Itraconazole was first used to treat fungal infections. However, a medical finding more than ten years ago demonstrated that itraconazole is highly effective in treating a variety of cancers, including skin, prostate, and lung cancers. As a result, its prompt repurposing gave the medication fresh life. By blocking cellular growth pathways and preventing the development of new blood vessels, itraconazole treats cancer. Through direct action on the SMO protein, it suppresses the Hedgehog pathway. One essential transmembrane protein in the Hedgehog (HH) signaling pathway is Smoothened (SMO). A highly conserved signaling pathway, the Hedgehog-GLI (HH-GLI) pathway is essential for regulating tissue patterning and cell-to-cell contact. Cancer and birth abnormalities are caused by mutations in proteins that transmit HH signals between cells. The various anti-cancer properties of itraconazole have been explained by a number of different modes of action. These consist of: suppression of the hedgehog pathway, Induction of autophagy, Multidrug resistance reversal and Anti-angiogenesis.

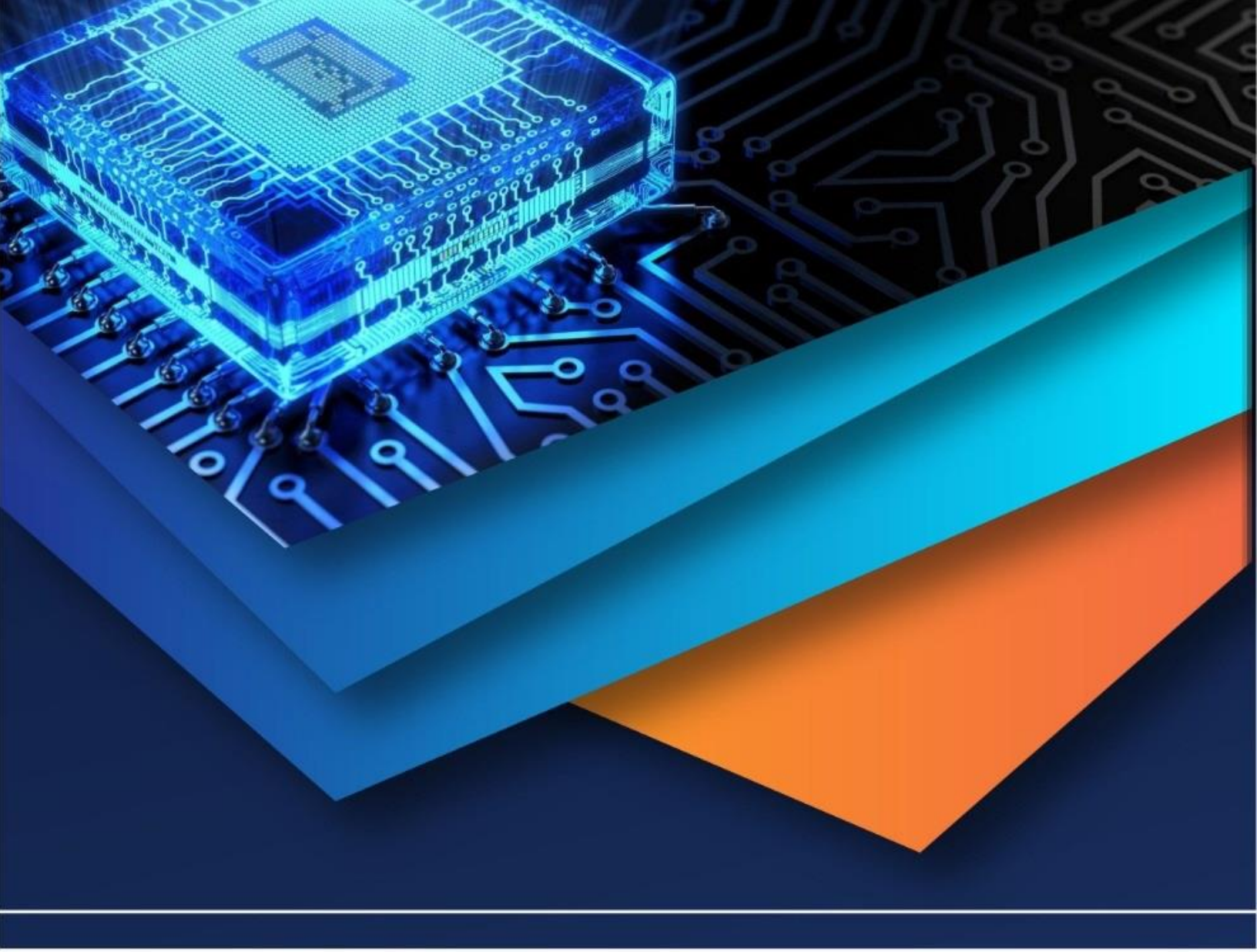
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